

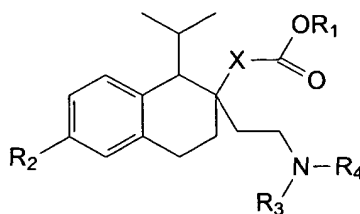
Claims

We claim:

1. A calcium channel blocker compound having at least one of the following characteristics:

- a. the compound is metabolized both by CYP450 and by a non-oxidative metabolic enzyme or system of enzymes;
- b. the compound has a short (up to four (4) hours) non-oxidative metabolic half-life;
- c. the compound contains a hydrolysable bond that can be cleaved non-oxidatively by hydrolytic enzymes;
- d. the primary metabolites of the compound result from the non-oxidative metabolism of the compound;
- e. the primary metabolites are soluble in water at physiological pH;
- f. the primary metabolites have negligible inhibitory activity at the IK_R (HERG) channel at normal therapeutic concentration of the parent drug in plasma;
- g. the compound, as well as the metabolites thereof, does not cause metabolic DDI when co-administered with other drugs; and
- h. the compound, as well as metabolites thereof, does not elevate LFT values when administered alone.

2. The compound, according to claim 1, having the following structure:



wherein:

X = a bond, (CH₂)_n, O, S, or O(CH₂)_n,

wherein n = 1-6;

$R_1 = C_{1-6}$ alkyl, optionally substituted with OH or NH_2 ;

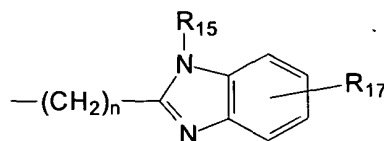
$R_2 = F$ or $COOR_5$,

wherein R_5 is C_{1-6} alkyl, optionally substituted with OH or NH_2 ;

$R_3 = CH_3$ or $(CH_2)_n - COOR_6$,

wherein $n = 1-6$ and R_6 is C_{1-6} alkyl, optionally substituted with OH or NH_2 ;

$R_4 = (CH_2)_n - COR_7R_8$, $-(CH_2)_n - R_{10}R_{11}$ or



$R_7 = O$, NH , or NR_9 ,

$R_8 =$ optionally substituted aryl or heterocycle,

$R_9 = C_{1-6}$ alkyl,

$R_{10} = O$, S , SO , SO_2 , NH , NR_{12} or $N(CH_2)_m COOR_{13}$,

$R_{11} =$ aryl or heterocyclyl optionally substituted with $(CH_2)_n COOR_{14}$,

$R_{12} = C_{1-6}$ alkyl, optionally substituted with OH or NH_2 ,

$R_{13} = C_{1-6}$ alkyl, optionally substituted with OH or NH_2 ,

$R_{14} = C_{1-6}$ alkyl, optionally substituted with OH or NH_2 ,

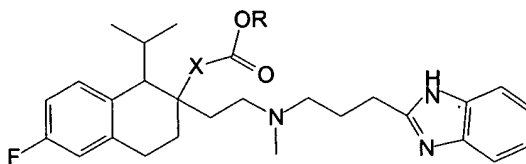
$R_{15} = (CH_2)_n COOR_{16}$,

$R_{16} = C_{1-6}$ alkyl, optionally substituted with OH or NH_2 ,

$R_{17} =$ not present or $COOR_{18}$ wherein R_{18} is C_{1-6} alkyl, optionally substituted with OH or NH_2 , and

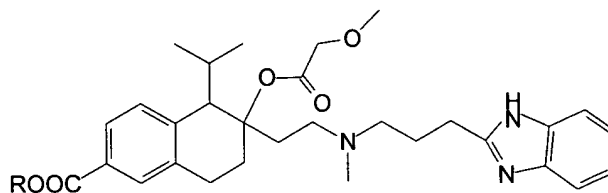
wherein $n = 1-6$.

3. The compound, according to claim 2, having a formula selected from the group consisting of:

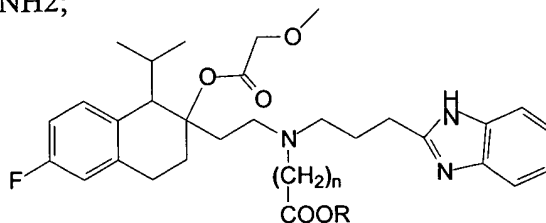


X = bond, CH₂, or OCH₂

R = lower alkyl optionally substituted OH or NH₂;

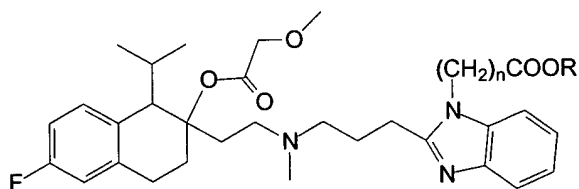


R = lower alkyl optionally substituted by OH or NH₂;



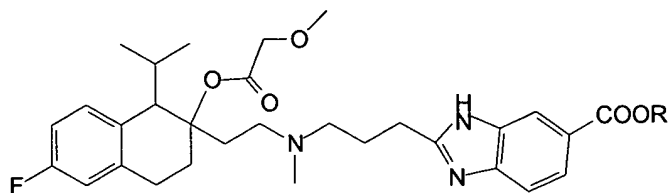
n = 1 to 3

R = lower alkyl optionally substituted by OH or NH₂;

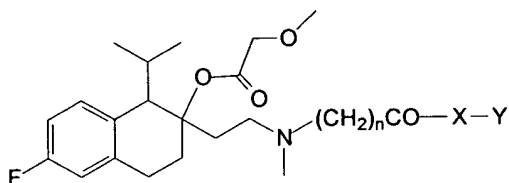


n = 1 to 3

R = lower alkyl optionally substituted by OH or NH₂;



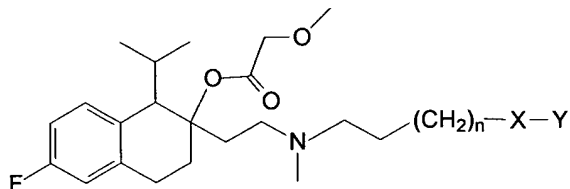
R = lower alkyl optionally substituted by OH or NH₂;



n = 1 to 3

X = O, NH, NR where R is lower alkyl

Y = optionally substituted aryl or heterocyclyl; and

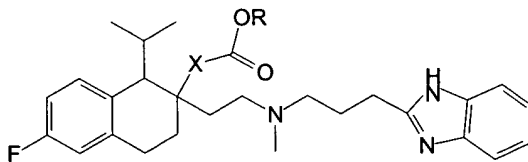


n = 0 to 2

X = O, S, SO, SO₂, NH NR or N(CH₂)_mCOOH where m is 0 or 2

Y = aryl or heterocyclyl substituted with (CH₂)_mCOOH where m is 0 to 2.

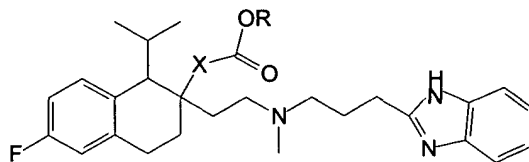
4. The compound, according to claim 3, having the following structure:



X = bond, CH₂, or OCH₂

R = lower alkyl optionally substituted OH or NH₂.

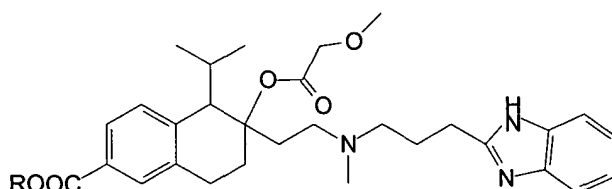
5. The compound, according to claim 3, having the following structure:



X = bond, CH₂, or OCH₂

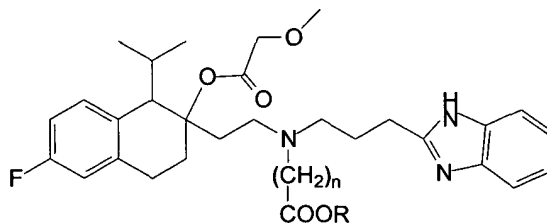
R = lower alkyl optionally substituted OH or NH₂.

6. The compound, according to claim 3, having the following structure:



R = lower alkyl optionally substituted by OH or NH₂.

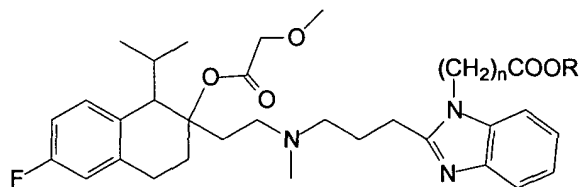
7. The compound, according to claim 3, having the following structure:



n = 1 to 3

R = lower alkyl optionally substituted by OH or NH₂.

8. The compound, according to claim 3, having the following structure:



n = 1 to 3

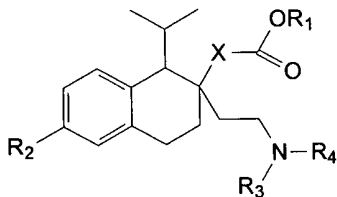
R = lower alkyl optionally substituted by OH or NH₂.

COCC(=O)O[C@]1(C)CCc2cc(F)ccc2[C@]1(CCN(C)CCCNc3nc4ccc(cc34)C(=O)OR)CCCC(C)C1(C)C2=CC=C(C=C2)C(F)=CC=C1C3(C)CC(C)CC3N(C)CCOC(=O)COXCN(C)CC(COC(=O)COC)c1ccc(F)cc1

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- c. the compound contains a hydrolysable bond that can be cleaved non-oxidatively by hydrolytic enzymes;
 - d. the primary metabolites of the compound result from the non-oxidative metabolism of the compound;
 - e. the primary metabolites are soluble in water at physiological pH;
 - f. the primary metabolites have negligible inhibitory activity at the IK_R (HERG) channel at normal therapeutic concentration of the parent drug in plasma;
 - g. the compound, as well as the metabolites thereof, does not cause metabolic DDI when co-administered with other drugs; and
 - h. the compound, as well as metabolites thereof, does not elevate LFT values when administered alone;
- wherein said composition further comprises a pharmaceutical carrier.

13. The pharmaceutical composition, according to claim 12, wherein said compound has the following structure:



wherein:

X = a bond, $(CH_2)_n$, O, S, or $O(CH_2)_n$,

wherein n = 1-6;

R_1 = C_{1-6} alkyl, optionally substituted with OH or NH_2 ;

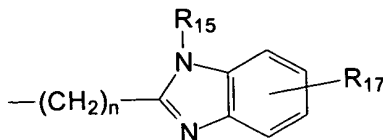
R_2 = F or $COOR_5$,

wherein R_5 is C_{1-6} alkyl, optionally substituted with OH or NH_2 ;

R_3 = CH_3 or $(CH_2)_n - COOR_6$,

wherein n = 1-6 and R_6 is C_{1-6} alkyl, optionally substituted with OH or NH_2 ;

R_4 = $(CH_2)_n - COR_7R_8$, $-(CH_2)_n - R_{10}R_{11}$ or



$R_7 = O, NH, \text{ or } NR_9,$

$R_8 = \text{optionally substituted aryl or heterocycle,}$

$R_9 = C_{1-6} \text{ alkyl,}$

$R_{10} = O, S, SO, SO_2, NH, NR_{12} \text{ or } N(CH_2)_m COOR_{13},$

$R_{11} = \text{aryl or heterocyclyl optionally substituted with } (CH_2)_n COOR_{14},$

$R_{12} = C_{1-6} \text{ alkyl, optionally substituted with OH or } NH_2,$

$R_{13} = C_{1-6} \text{ alkyl, optionally substituted with OH or } NH_2,$

$R_{14} = C_{1-6} \text{ alkyl, optionally substituted with OH or } NH_2,$

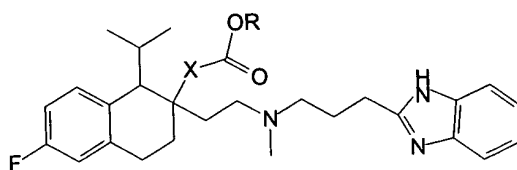
$R_{15} = (CH_2)_n COOR_{16},$

$R_{16} = C_{1-6} \text{ alkyl, optionally substituted with OH or } NH_2,$

$R_{17} = \text{not present or } COOR_{18} \text{ wherein } R_{18} \text{ is } C_{1-6} \text{ alkyl, optionally substituted with OH or } NH_2, \text{ and}$

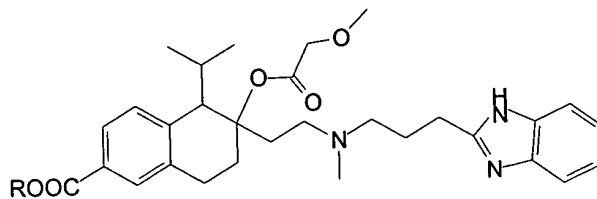
wherein $n = 1-6.$

14. The composition, according to claim 13, comprising a compound having a formula selected from the group consisting of:

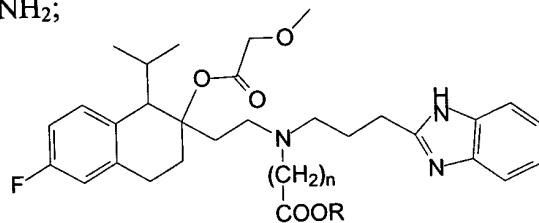


X = bond, CH₂, or OCH₂

R = lower alkyl optionally substituted OH or NH₂;

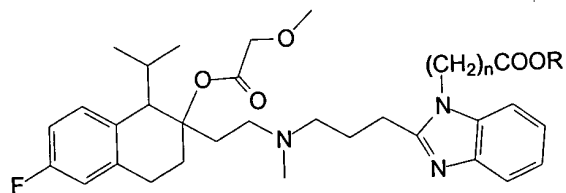


R = lower alkyl optionally substituted by OH or NH₂;



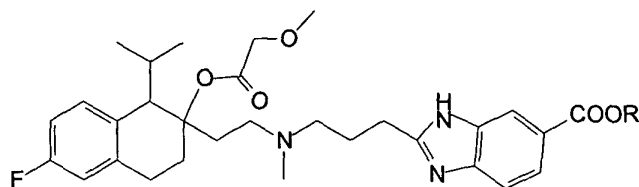
n = 1 to 3

R = lower alkyl optionally substituted by OH or NH₂;

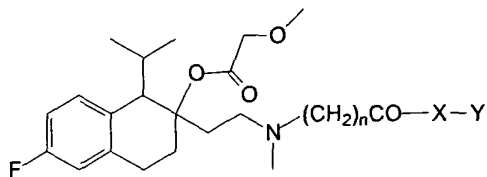


n = 1 to 3

R = lower alkyl optionally substituted by OH or NH₂;



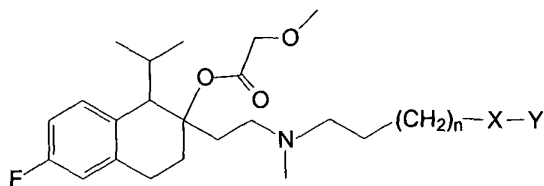
R = lower alkyl optionally substituted by OH or NH₂;



n = 1 to 3

X = O, NH, NR where R is lower alkyl

Y = optionally substituted aryl or heterocyclyl; and

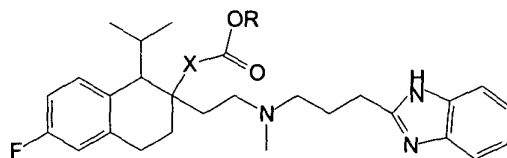


n = 0 to 2

X = O, S, SO, SO₂, NH NR or N(CH₂)_mCOOH where m is 0 or 2

Y = aryl or heterocyclyl substituted with (CH₂)_mCOOH where m is 0 to 2.

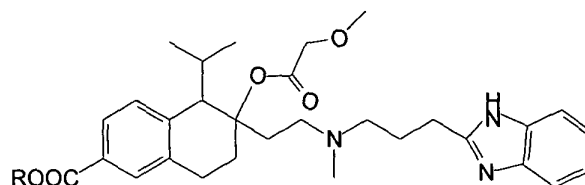
15. The composition, according to claim 14, comprising a compound having the following structure:



X = bond, CH₂, or OCH₂

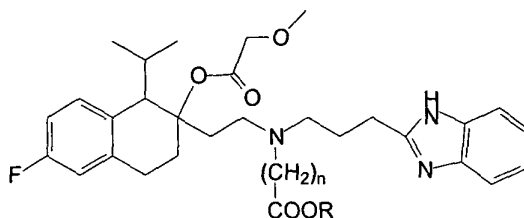
R = lower alkyl optionally substituted OH or NH₂.

16. The composition, according to claim 14, having the following structure:



R = lower alkyl optionally substituted by OH or NH₂.

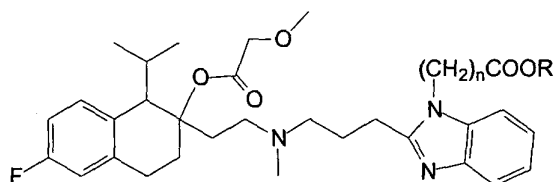
17. The composition, according to claim 14, having the following structure:



n = 1 to 3

R = lower alkyl optionally substituted by OH or NH₂.

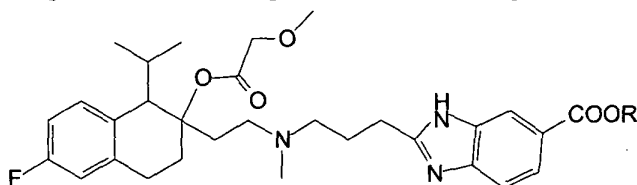
18. The composition, according to claim 14, having the following structure:



n = 1 to 3

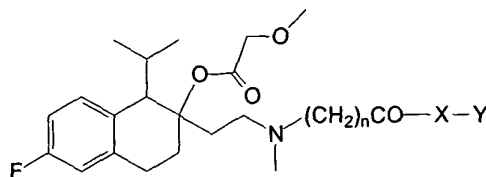
R = lower alkyl optionally substituted by OH or NH₂.

19. The composition, according to claim 14, having the following structure:



R = lower alkyl optionally substituted by OH or NH₂.

20. The composition, according to claim 14, having the following structure:

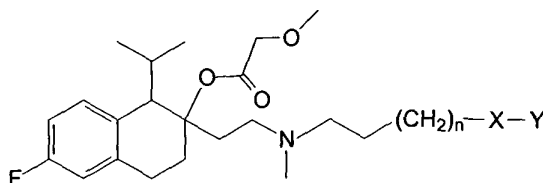


$n = 1 \text{ to } 3$

$X = O, NH, NR$ where R is lower alkyl

$Y = \text{optionally substituted aryl or heterocyclyl.}$

21. The composition, according to claim 14, having the following structure:



$n = 0 \text{ to } 2$

$X = O, S, SO, SO_2, NH, NR$ or $N(CH_2)_mCOOH$ where m is 0 or 2

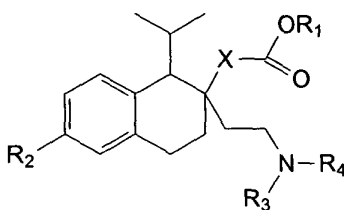
$Y = \text{aryl or heterocyclyl substituted with } (CH_2)_mCOOH \text{ where } m \text{ is } 0 \text{ to } 2.$

22. A method for blocking a calcium channel in a patient in need of such treatment wherein said method comprises administering to said patient a calcium channel blocking compound having at least one of the following characteristics:

- a. the compound is metabolized both by CYP450 and by a non-oxidative metabolic enzyme or system of enzymes;
- b. the compound has a short (up to four (4) hours) non-oxidative metabolic half-life;
- c. the compound contains a hydrolysable bond that can be cleaved non-oxidatively by hydrolytic enzymes;
- d. the primary metabolites of the compound result from the non-oxidative metabolism of the compound;
- e. the primary metabolites are soluble in water at physiological pH;

- f. the primary metabolites have negligible inhibitory activity at the IK_R (HERG) channel at normal therapeutic concentration of the parent drug in plasma;
- g. the compound, as well as the metabolites thereof, does not cause metabolic DDI when co-administered with other drugs; and
- h. the compound, as well as metabolites thereof, does not elevate LFT values when administered alone.

23. The method, according to claim 22, wherein said compound has the following structure:



wherein:

$X = \text{a bond, } (CH_2)_n, O, S, \text{ or } O(CH_2)_n,$

wherein $n = 1-6$;

$R_1 = C_{1-6}$ alkyl, optionally substituted with OH or NH_2 ;

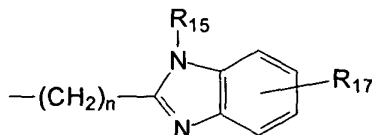
$R_2 = F$ or $COOR_5$,

wherein R_5 is C_{1-6} alkyl, optionally substituted with OH or NH_2 ;

$R_3 = CH_3$ or $(CH_2)_n - COOR_6$,

wherein $n = 1-6$ and R_6 is C_{1-6} alkyl, optionally substituted with OH or NH_2 ;

$R_4 = (CH_2)_n - COR_7R_8, -(CH_2)_n - R_{10}R_{11}$ or



$R_7 = O, NH, \text{ or } NR_9,$

R_8 = optionally substituted aryl or heterocycle,

R_9 = C_{1-6} alkyl,

R_{10} = O, S, SO, SO_2 , NH, NR_{12} or $N(CH_2)_m COOR_{13}$,

R_{11} = aryl or heterocyclyl optionally substituted with $(CH_2)_n COOR_{14}$,

R_{12} = C_{1-6} alkyl, optionally substituted with OH or NH_2 ,

R_{13} = C_{1-6} alkyl, optionally substituted with OH or NH_2 ,

R_{14} = C_{1-6} alkyl, optionally substituted with OH or NH_2 ,

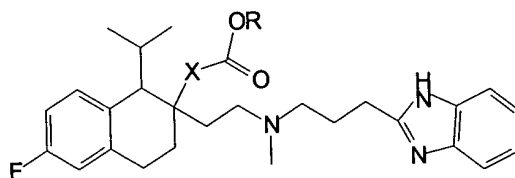
R_{15} = $(CH_2)_n COOR_{16}$,

R_{16} = C_{1-6} alkyl, optionally substituted with OH or NH_2 ,

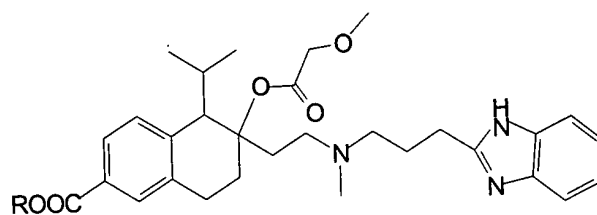
R_{17} = not present or $COOR_{18}$ wherein R_{18} is C_{1-6} alkyl, optionally substituted with OH or NH_2 , and

wherein $n = 1-6$.

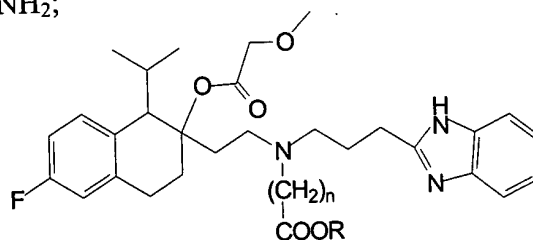
24. The method, according to claim 23, wherein said compound has a formula selected from the group consisting of:



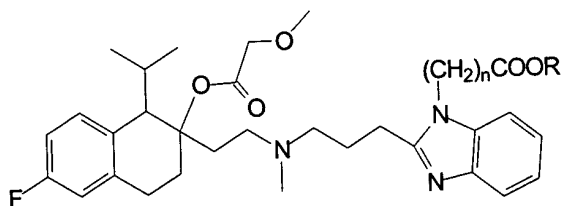
X = bond, CH₂, or OCH₂
 R = lower alkyl optionally substituted OH or NH₂;



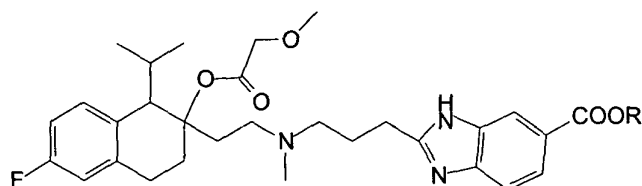
R = lower alkyl optionally substituted by OH or NH₂;



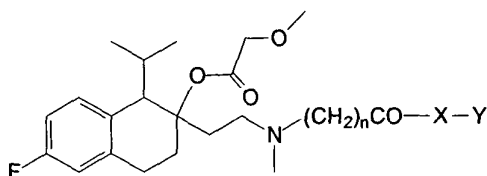
n = 1 to 3
 R = lower alkyl optionally substituted by OH or NH₂;



n = 1 to 3
 R = lower alkyl optionally substituted by OH or NH₂;



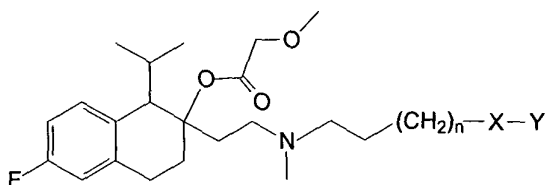
R = lower alkyl optionally substituted by OH or NH₂;



n = 1 to 3

X = O, NH, NR where R is lower alkyl

Y = optionally substituted aryl or heterocyclyl; and

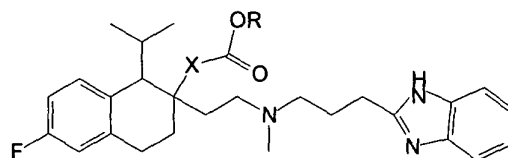


n = 0 to 2

X = O, S, SO, SO₂, NH NR or N(CH₂)_mCOOH where m is 0 or 2

Y = aryl or heterocyclyl substituted with (CH₂)_mCOOH where m is 0 to 2.

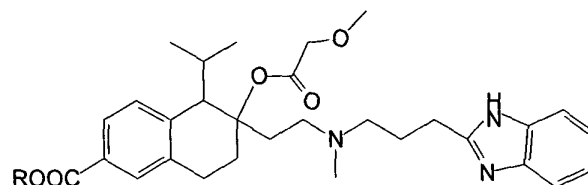
25. The method, according to claim 24, wherein said compound has the following structure:



X = bond, CH₂, or OCH₂

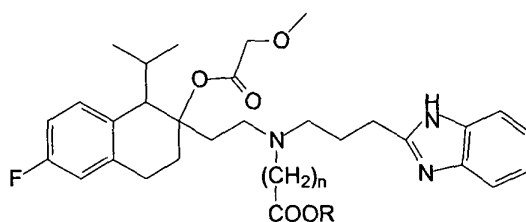
R = lower alkyl optionally substituted OH or NH₂.

26. The method, according to claim 24, wherein said compound has the following structure:



R = lower alkyl optionally substituted by OH or NH₂.

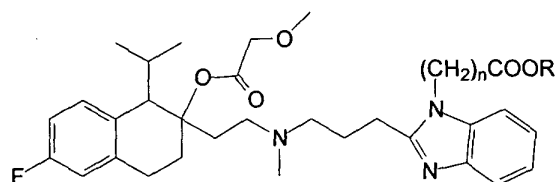
27. The method, according to claim 24, wherein said compound has the following structure:



n = 1 to 3

R = lower alkyl optionally substituted by OH or NH₂.

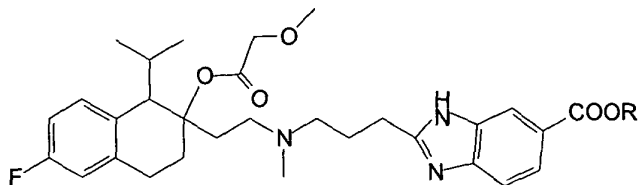
28. The method, according to claim 24, wherein said compound has the following structure:



n = 1 to 3

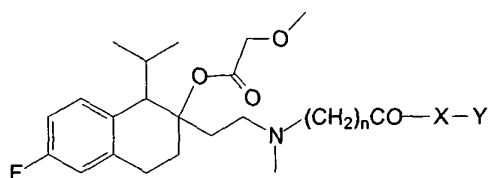
R = lower alkyl optionally substituted by OH or NH₂.

29. The method, according to claim 24, wherein said compound has the following structure:



R = lower alkyl optionally substituted by OH or NH₂.

30. The method, according to claim 24, wherein said compound has the following structure:

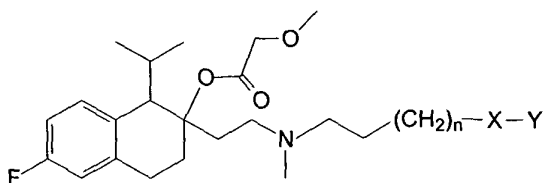


n = 1 to 3

X = O, NH, NR where R is lower alkyl

Y = optionally substituted aryl or heterocyclyl.

31. The method, according to claim 24, wherein said compound has the following structure:



n = 0 to 2

X = O, S, SO, SO₂, NH NR or N(CH₂)_mCOOH where m is 0 or 2

Y = aryl or heterocyclyl substituted with (CH₂)_mCOOH where m is 0 to 2.

32. The method, according to claim 22, wherein the patient is a human.

33. The method, according to claim 22, wherein said method is used to treat a condition selected from the group consisting of hypertension, angina, ischemia, arrhythmia, congestive heart failure, and cardiac insufficiency.